Remarks

Claim 1 has been amended to specify that the tissue overexpresses the digestive enzyme. Support for the amendment is found at least in the claims as originally filed.

Claim 13 has been amended to specify that the patient has a disorder that is characterized by overexpression of a digestive enzyme. Support for the amendment is found in the claims as originally filed and at page 5, lines 3-12.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 12, and 13 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Applicants respectfully traverse this rejection. To the extent the rejection confuses written description with enablement, this rejection is also traversed.

Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (the Federal Circuit) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); *See also In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970); *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 U.S.P.Q. 659 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the

art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). In addition, as affirmed by the Federal Circuit in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well-known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. *See In re Wands*, 858 F.2d 731, 735, 736-737, 8 U.S.P.Q.2d 1400, 1402, 1404 (Fed. Cir. 1988). A determination of undue experimentation is a conclusion based on weighing many factors, not just a single factor. Many of these factors have been summarized in *In re Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986) and are set forth in *In re Wands*. They are: (1) The quantity of experimentation necessary (time and expense); (2) The amount of direction or guidance presented; (3) The presence or absence of working examples of the invention; (4) The nature of the invention; (5) The state of the prior art; (6) The relative skill of those in the art; (7) The predictability or unpredictability of the art; and (8) The breadth of the claims. The M.P.E.P. explains that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." (M.P.E.P. § 2164.01 (a)). Thus, a conclusion of nonenablement must be based on the evidence as a whole, as related to these factors. (*Id.*)

In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970). The fact that some experimentation is necessary does

not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. & Int. 1982).

There is no requirement for examples. *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970). Further, patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The first paragraph of Section 112 provides that the "specification shall contain a written description of the invention..." 35 U.S.C. § 112 (2005). "The description requirement's purposes are to assure that the applicant was in full possession of the claimed subject matter on the application filing date and to allow other inventors to develop and obtain patent protection for later improvements and subservient inventions that build on applicant's teachings." 3-7 Chisum on Patents § 7.04 (2005), citing *Fields v. Conover*, 443 F.2d 1386, 170 U.S.P.Q. 276 (CCPA 1971).

Legal Standard for Written Description

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *See* M.P.E.P. § 2163(I). Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Id.*, citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *Pfaff v. Wells Electronics, Inc.*, 55 U.S. at 66, 119 S.Ct. at 311, 48 USPQ2d at 1646. As noted in a recent decision by the Board of Appeals and Interferences, the written description requirement does not require a description of the complete structure of every species within a chemical genus. (*see Utter v. Hiraga*, 845 F.2d 993, 998, 6 U.S.P.Q.2d 1709, 1714 (Fed. Cir. 1988), stating "A specification may, within the meaning of 35 U.S.C. § 112, para. 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.").

A specification may describe an actual reduction to practice by showing that the inventor constructed *an embodiment* or performed *a process* that met all the limitations of the claim and

determined that the invention would work for its intended purpose. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998) (emphasis added). Although reduction to practice often provides the best evidence that an invention is complete, actual reduction to practice is not required by the written description requirement. An applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In *Falkner*, the Federal Circuit recently addressed the issue of written description in an appeal from an interference. *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006). The issue was whether the applicant's priority applications adequately described and enabled a poxvirus-based vaccine. The Federal Circuit reiterated that "[t]he 'written description requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves to demonstrate that the patentee was in possession of the invention that is claimed." *Falkner* at 1366. The Federal Circuit also clarified that with regard to the written description requirement: (1) examples are not necessary to support the adequacy of the a written description; (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. *Falkner* at 1366.

With respect to original claims, the M.P.E.P. states that "there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." M.P.E.P. § 2163(I) (A), *citing In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

Analysis

Claims 1, 2, 12, and 13 are enabled and comply with written description

The Examiner alleges that claims 1, 2, 12, and 13 are not enabled because the specification does not reasonably provide enablement for a linker that is cleaved when the conjugate is exposed to a digestive enzyme chosen from serine proteases and matrix metalloproteinases.

The Examiner is not applying the appropriate legal standard. As detailed above, the test for enablement is whether one of ordinary skill in the art could make and use the claimed compositions and methods without *undue* experimentation. Whether or not experimentation is undue is a conclusion based on weighing *many* factors, not just a *single* factor, as presented by the Examiner. There is no requirement that all embodiments within a genus be enabled to meet the standard for enablement.

A proper analysis of the *Wands* factors shows that the claimed compositions and methods are enabled. As discussed in detail below, based on the amount of guidance provided in the specification, the quantity of experimentation necessary, the presence of working examples, and

the breadth of the claims, one of ordinary skill in the art would be able to make and use the claimed compositions without undue experimentation.

The breadth of the claims

The claims are directed to a conjugate containing a polymeric carrier, a drug molecule, and a linker that includes a first and a second end, wherein the linker includes an oligopeptide recognition segment that is cleaved when the conjugate is exposed to a digestive enzyme. The conjugates cannot contain any linker; rather the linker is limited to those linkers, which contain an oligopeptide recognition segment that is cleaved by a digestive enzyme selected from serine proteases and matrix metalloproteinases.

The state of the prior art

In the Office Actions mailed March 21, 2007 and September 28, 2007, the Examiner alleged that the state of the art of drug conjugates comprising peptide linkers is high; while the state of the art for using peptide linkers cleavable by digestive enzymes is very low or does not exist (*see* page 5 of the Office Action mailed on March 21, 2007). The Examiner asserts that this is verified by applicants' own specification which states "a digestive enzyme that cleaves oligopeptides will typically exhibit strong selectivity for oligopeptides that include one or a small subset of amino acid sequences called recognition sequences". Applicants' respectfully disagree. As discussed below, the specification cites several references which disclose methods for determining cleavage motifs for digestive enzymes, such as substrate phase display libraries (Matthew and Wells, *Science*, 260:1113 (1993)); position scanning peptide libraries (Rano *et al.*,

Chem. Biol., 4:149 (1996)); and mixture-based peptide libraries (Turk *et al.*, *Nature Biotechnology*, 19:661 (2001)) (page 17, lines 1-17).

As noted in *Ex parte Jackson*, the test for enablement is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. Pat. App. & Int. 1982). The references cited above provide more than a reasonable amount of guidance for determining the recognition sequences in the claimed conjugates and describe methods that would be routine to one of ordinary skill in the art.

The amount of direction or guidance presented in the application and the quantity of experimentation necessary

Patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

The Examiner alleges that the specification as filed "does not speak on or show any working examples or studies performed on other cleavable peptide sequences". The Examiner is applying the wrong legal standard. Applicants are not required to show working Examples or studies performed on other linkers. The standard is that one of ordinary skill in the art could practice the claimed invention without undue experimentation.

First, the enzymes specified in the claims are known and well characterized. Their substrates are also known. One skilled in the art would have no difficulty in determining additional sequences that can be cleaved by the enzymes specified in claim 1. Moreover, the specification provides numerous details of how to make and use the claimed subject matter. The specification discloses that a variety of methods known in the art can be used to determine the cleavage motif of a target enzyme when it is not yet known and cites several references describing these methods. Such methods include substrate phase display libraries (Matthew and Wells, *Science*, 260:1113 (1993)); position scanning peptide libraries (Rano *et al.*, *Chem. Biol.*, 4:149 (1996)); and mixture-based peptide libraries (Turk *et al.*, *Nature Biotechnology*, 19:661 (2001)) (page 17, lines 1-17).

The specification discloses that phage display method has been used to determine peptide substrates for a number of proteases, for example, plasmin (Hervio *et al.*, *Chem. Biol.*, 7:443 (2000)); tissue-type plasminogen activator (Ding *et al.*, *Proc. Natl. Acad. Sci. USA*, 92:7627 (1995) and Ke *et al.*, *J. Biol. Chem.*,272:16603 (1997)); prostate-specific antigen (Coombs *et al.*, *Chem. Biol.* 5:475 (1998)); and membrane type-1 matrix metalloproteinases (Ohkubo *et al.*, *Biochem. Biophys. Res. Commun.*, 266:308 (1999)) (page 17, line 18 to page 18, line 2). These references disclose several oligopeptides which are substrates for plasmin, plasminogen activator, prostate-specific antigen, and membrane type-1 matrix metalloproteinases. Appendix A lists the cleavage motifs for a range of secreted or membrane bound proteases that are overexpressed in certain tumor tissues.

The specification discloses screening techniques which identify sequences which are labile to the target enzyme but resistant to serum proteins (page 18, lines 16 and 17). The specification discloses methods for making the conjugates as well as assays for evaluating whether a particular linker is suitable for use in a conjugate (*see* the Examples). For example, sets of polymer-linker-drug conjugates or polymer-linker-dye conjugates may be synthesized for kinetic analysis to determine the kinetics of enzyme cleavage (page 19, lines 6-16).

The Examiner is silent regarding the references and assays described except to say that they are undue experimentation. How, the Examiner provides no evidence whatsoever to support such an allegation. The Examiner cites the Genentech case, which states that "a patent is not a hunting license, or a reward for search, but compensation for its successful conclusion" as support for his position. However, the Genentech case has no bearing on the present claims. As discussed above, Applicants have clearly shown how one of ordinary skill in the art can determine the cleavage motif of a target enzyme when it is not yet known; determine peptide substrates for known enzymes, such as proteases; and identify sequences which are labile to a target enzyme but resistant to serum proteins without undue experimentation.

The presence of working examples

Although it is not required under 35 U.S.C. §112, first paragraph, the specification provides working examples of the claimed compositions and methods. The Examiner alleges that the Examples do not provide guidance on the use of other peptide linkers and the enzymes which cleave those linkers. Once again, the Examiner is not using the correct legal standard.

As discussed above, Appendix A and the references cited in the specification describe peptide substrates for a number of proteases. Further, the specification discloses a number of methodologies for generating peptide sequences that can be cleaved by known or unknown enzymes.

Examples 1, 5, 6, 7, and 8 describe the synthesis of dextran-oligopeptide-drug conjugates containing doxorubicin or methotrexate. The oligopeptides were synthesized using conventional solid-phase techniques and the conjugates may be synthesized using traditional techniques of peptide coupling and dextran modification. This methodology can be used to prepare conjugates containing other peptide linkers since peptides generally contain the same or similar functional groups.

Examples 2 and 9 describe the peptidyl release or doxorubicin and methotrexate in the presence of MMP-2. Examples 3 and 10 describe *in vitro* cytotoxicity studies of dextran-oligopeptide-drug conjugates containing doxorubicin and methotrexate. Examples 4 and 11 describe serum stability studies of dextran-oligopeptide-drug conjugates containing doxorubicin and methotrexate. These assays can be used to evaluate the release of an active agent from other peptide linkers, the cytotoxicity of conjugates containing other peptide linkers, and the serum stability of conjugates containing other peptide linkers. The Examiner has provided no evidence that the methods of synthesis and/or assays described in the Examples cannot be used with other peptide linkers.

Conclusion

Applying the *Wands* factors, one sees that the specification provides a high level of detail for the claimed conjugates and methods of making and characterizing thereof. The level of skill in the art is high, and one of ordinary skill in the art is aware of a variety of oligopeptides which are substrates for plasmin, plasminogen activator, prostate-specific antigen, and membrane type-1 matrix metalloproteinases and methods for generating such peptides. The claims are not overly broad. Therefore, one of ordinary skill in the art could make and use the claimed compositions without undue experimentation. The arguments provided above are also applicable to the lack of written description rejection. Therefore, claims 1, 2, 12, and 13 are enabled and comply with the written description requirement.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 4 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

Legal Standard

Exxon Research and Engineering Company v. United States, 265 F.3d 1371 (Fed. Cir. 2001), stated the standard to be as follows: "If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2." *Id. citing Miles Labs, Inc., v. Shandon, Inc.,* 997 F.2d 870 (Fed. Cir. 1994). The court further stated that claims do not have to be plain on their face to be definite. Rather, "the claims need be amenable to construction, however difficult that task may be. If the meaning

of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds." *Id.*

Bausch & Lomb, Inc., v. Alcon Laboratories, Inc., 79 F.Supp 243 (W.D. NY 1999), contains general information on the purpose of the definiteness requirement and refers to the ruling in *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.,* 758 F.2d 613 (Fed. Cir. 1985), which held that "if the claims, read in the light of the specifications, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *Id.* at 245. Further, "that some claim language may not be precise...does not automatically render a claim invalid." *Id.* at 247.

To that end, *Solomon v. Kimberly-Clark Corp.,* 216 F.3d 1372 (Fed. Cir. 2000) held that to determine if a claim is definite requires "an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more." *Id.* at 1379 *citing Personalized Media v. ITC, 161 F.3d 696 (Fed. Cir. 1998).*

Analysis

The Examiner also alleged that the phrase "size of the polymeric carrier is larger than the renal excretion limit" in claim 4 is indefinite. Specifically, the Examiner alleges that this phrase

is not defined in the claim and that the specification does not provide a standard for ascertaining the requisite degree. The Examiner is incorrect.

The specification discloses that, in certain embodiments, the polymeric carrier allows conjugates and hence drugs to circulate longer in plasma by decreasing renal excretion and liver clearance (page 9, lines 6-9). The specification cites an article by Hashida and Takakura which relates the physiological features of the liver and kidneys to the clearance data obtained with macromolecules (page 9, lines 9-12). The specification discloses that glomerular capillaries in the kidneys are fenestrated, with pores having radii estimate at 20-30 nm (page 9, lines 13-14). Their basement membranes act as a size and charge barrier, which appears to hinder the transport of particles above 6 nm (page 9, lines 14-15). Consistent with these features, macromolecules with sizes above about 6 nm (MW ~ 50,000 Daltons) exhibit marked inhibition on renal clearance (page 9, lines 15-16). This value, however, is not an absolute.

Rypáček *et al.*, a copy of which is enclosed, discloses that clearance of macromolecular models from serum is mainly molecular weight controlled, while the retention of macromolecules possessing the same molecular weight by the kidneys is strongly affected by chemical modification (Rypáček *et al.*, *Arch. Eur. J. Physiology*, Vol. 392, No. 3, 211-217 (1981)). Therefore, the renal excretion limit is dependent both on the molecular weight of the macromolecule as well as the chemical composition of the macromolecule. One of ordinary skill in the art would understand the phrase "renal excretion limit" to mean the size and/or molecular

weight below which a given polymer is readily cleared from the renal system and that the size may vary from one polymer to another.

The claims, when read in the light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and the language is as precise as the subject matter permits. Accordingly, claim 4 is definite.

Rejection Under 35 U.S.C. § 102

Claims 1-6, 9-13, 17-22, 29, 33, 39, 43, 47-52, and 54-56 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 01/68145 to Copeland *et al.* ("Copeland"). Applicants respectfully traverse this rejection.

Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc. v Monoclonal Antibodies Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986); *Scripps Clinic & Research Found v. Genentech Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 U.S.P .Q.2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. [...] There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps*:

[A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

Id.

For a prior art reference to anticipate a claim, it must enable a person of ordinary skill in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. [...] [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.*, 231 U.S.P.Q. 649, 653 (Fed. Cir. 1986).

Analysis

Copeland does not disclose or suggest compositions containing a polymeric carrier as required by the independent claims

Copeland describes compositions containing antineoplastic agents conjugated to enzyme cleavable peptides containing the amino acid recognition sequence of a membrane-bound and/or

cell secreted peptidase (abstract). The peptide is capped with a capping group (page 5, line 31). Suitable capping groups are discussed beginning at page 42, line 26. Copeland discloses that polyethylene glycols having the formula

$$H_3OCO\text{-}(CH_2CH_2O)_t\text{-}CH_2C(=O)\text{-}$$

where t is 1 to 10, preferably t is 1, 2, 3, or 4, more preferably where t is 1 or 2 can be used as amino-capping groups (page 43, lines 17-22). Copeland states that unless otherwise specified, "polyethylene glycol", or "PEG" or "Peg" as an amino capping group having the formula shown below (page 43, lines 20-22):

$$H_3COCH_2CH_2OCH_2CH_2OCH_2C(=O)\text{-}$$

This molecule contains only two monomer units.

The molecules disclosed in Copeland are oligomers, not polymers. An oligomer is defined as a polymer containing from 2-10 repeat units (*see* the definition of oligomer from Seymour and Carraher, Polymer Chemistry, Dekker Publishing (1993), a copy of which is enclosed). Therefore, the PEG end capping units disclosed in Copeland, which contain between 2 and 10 monomer units, are outside the scope of the claimed conjugates.

The Examiner also alleges that since the enzyme selective peptide sequences are in a larger peptide, the rest of the peptide not cleaved by the digestive enzyme can be considered as a polymeric carrier since peptides are poly amino acids. The claimed conjugates require at least three distinct components: a polymeric carrier, a drug, and a linker which contains an oligopeptide recognition segment, wherein one end of the linker is bound to the polymeric carrier

and the other end is bound to the drug. The linker and the polymer cannot be the same molecule. Following the Examiner's argument, Copeland would not contain a distinct polymeric carrier and a distinct linker as required by the claims.

Copeland does not disclose each and every element of the claims. Accordingly, claims 1-6, 9-13, 17-22, 29, 33, 39, 43, 47-52, and 54-56 are novel over Copeland.

Copeland does not disclose or suggest polymeric carriers having a size larger than the renal excretion limit as required in claim 4

Claim 4 depends from claim 1 and specifies that the size of the polymeric carrier is larger than the renal excretion limit. The specification discloses that macromolecules with sizes above, for example, 6 nm (MW ~ 50,000 Daltons) exhibit marked inhibition on renal clearance. The end capping groups disclosed in Copeland have molecular weights between 145 and 513, which is well below the renal excretion limit. Therefore, the carrier described in Copeland would be readily cleared by the renal system. Accordingly, claim 4 is novel over Copeland.

Rejection Under 35 U.S.C. § 103

Claims 1-6, 9-14, 17-22, 29, 33, 39, 43, 44, 47-52, and 54-56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/56425 to Duncan, in view of Copeland. Applicants respectfully traverse this rejection.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the

level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The Supreme Court did not obviate the requirement for the references to provide some motivation to combine as applicants have done, with a reasonable expectation of success. Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

> "The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . . There is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Analysis

As discussed above, the United States Supreme Court in *KSR* reaffirmed the *Graham* factors an obviousness analysis. The *Graham* factors are analyzed below:

(a) Determining the scope and contents of the prior art

The scope and contents of the prior art must be made *at the time the invention was made.* The requirement "at the time the invention was made" is to avoid impermissible hindsight. "It is difficult but necessary that the decision maker forget what he or she has been taught [...] about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983).

Duncan describes a product or kit containing two components, i.e., two pharmaceutical compositions that are arranged or otherwise adapted for sequential administration to a human or

animal (page 3, line 36 to page 4, line 2). The first component is an enzyme conjugate, e.g., a composition that contains a pharmaceutically acceptable excipient and an enzyme conjugate (page 4, lines 2-5). The enzyme conjugate may consist of an enzyme covalently bound to a polymeric or other carrier, such that the enzyme conjugate retains its enzyme activity (page 4, lines 5-7). The second component is a prodrug, e.g., a composition that contains a pharmaceutically acceptable excipient and a prodrug (page 4, lines 8-10). The prodrug can be conjugated to a polymeric carrier via an peptide linker. Duncan does not disclose a conjugate containing a linker that contains an oligopeptide recognition segment that is cleaved when the conjugate is exposed to a digestive enzyme *that is overexpressed by a tissue*. Further, Duncan does not disclose or suggest the linkers defined in claims 15 and 16.

Copeland is discussed above. Copeland does not disclose or suggest a composition containing a polymeric carrier as required by the claims. Further, Copeland does not disclose or suggest the linkers defined in claims 15 and 16.

(b) Ascertaining the differences between the prior art and the claims

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 U.S. P.Q. 698 (Fed. Cir. 1983).

The Claimed Compositions and Methods

The claims define a conjugate for use in targeting a drug to a tissue, wherein a digestive enzyme is overexpressed by the tissue. As discussed in the specification, such conjugates allow the conjugate to circulate longer in plasma by decreasing renal excretion and liver clearance.

Independent claim 1 and its dependent claims, define conjugates for use in targeting a drug to a tissue, wherein the tissue overexpresses a digestive enzyme comprising:

a polymeric carrier;

a drug molecule; and

a linker that includes a first end and a second end, wherein the polymeric carrier is associated with the first end of the linker and the drug is associated with the second end of the linker

wherein the linker includes an oligopeptide recognition segment that is cleaved when the conjugate is exposed to the digestive enzyme, and

wherein the digestive enzyme is selected from the group consisting of serine proteases and matrix metalloproteinases.

Claim 12 defines a method of preparing a conjugate for use in targeting a drug to a tissue, wherein the tissue overexpresses a digestive enzyme, the method comprising:

providing a polymer carrier;

providing a drug molecule;

providing a linker that includes at least a first end and a second end, wherein the linker includes an oligopeptide recognition segment that is cleaved when the conjugate is exposed to the digestive enzyme; wherein the digestive enzyme us selected from the group consisting of serine proteases and matrix metalloproteinases;

associating the polymer carrier with the first end of the linker; and

associating the drug molecule with the second end of the linker.

Claim 13 and its dependent claims define a method of targeting a drug to a tissue in a patient, wherein a digestive enzyme is overexpressed in the extracellular space of the tissue, the method comprising the steps of:

providing a patient;

providing a pharmaceutical composition that comprises a pharmaceutically acceptable excipient and an effective amount of a conjugate; and

administering the pharmaceutical composition to the patient; wherein the conjugate comprises:

a polymeric carrier;

a drug molecule; and

a linker that includes a first end and a second end, wherein the polymeric carrier is associated with the first end of the linker and the drug is associated with the second end of the linker; wherein the linker includes an oligopeptide recognition segment that is cleaved when the

conjugate is exposed to the digestive enzyme; and wherein the digestive enzyme is selected from the group consisting of serine proteases and matrix metalloproteinases.

The claimed compositions require that the digestive enzyme is overexpressed **by the tissue**. In contrast, Duncan requires administration of an enzyme conjugate to achieve overexpression in the tissue.

One of ordinary skill in the art would not be motivated to combine Duncan and Copeland because Copeland teaches away from the use of polymeric carriers

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. See *United States v. Adams*, 383 U.S. 39, 52, 148 U.S.P.Q. (BNA) 479, 484, 15 L. Ed. 2d 572, 86 S. Ct. 708 (1966) ("known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness"); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550-51, 220 U.S.P.Q. (BNA) 303, 311 (Fed. Cir. 1983) (the totality of a reference's teachings must be considered), cert. denied, 469 U.S. 851 (1984); *In re Caldwell*, 50 C.C.P.A. 1464, 319 F.2d 254, 256, 138 U.S.P.Q. (BNA) 243, 245 (CCPA 1963) (reference teaches away if it leaves the impression that the product would not have the property sought by the applicant).

As discussed above, Copeland describes conjugates containing an anticancer agent and an enzyme-cleavable peptide linker. The linker can be **optionally modified** at the end not conjugated by the drug, typically the N-terminus (page 42, lines 19-22). Copeland discloses that such modifications can be for a number of reasons, for example, to increase plasma stability of the peptide against enzymatic degradation by non-selective enzymes in the plasma or to increase solubility (page 42, lines 22-24). Suitable capping groups include PEG oligomers, where the number of monomer units is from 1 to 10. The most preferred PEG capping group is where the number of monomer units is 1 or 2. In fact, Copeland defines "polyethylene glycol", or "PEG" or "Peg" as an amino capping group having the formula shown below:

$$H_3COCH_2CH_2OCH_2CH_2OCH_2C(=O)-$$

where the number of monomer units is two (page 43, lines 20-22).

A capping group containing an oligomer of PEG containing two monomer units is not a polymeric carrier. Further, the end capping groups described in Copeland are not sufficiently large to decrease renal excretion and liver clearance as sought by the applicants. A reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. The oligomers disclosed in Copeland are not likely to be productive of the result sought by the applicant. Accordingly, one would not be motivated to combine the conjugates of Duncan with the oligomers of Copeland to arrive at the claimed compositions. Accordingly, claims 1-6, 9-14, 17-22, 29, 33, 39, 43, 44, 47-52, and 54-56 are not obvious over Duncan in view of Copeland.

One of ordinary skill in the art would not be motivated to combine Duncan and Copeland because Duncan teaches away from administering a conjugate containing a linker that is cleaved by a digestive enzyme overexpressed by the tissue itself

As discussed above, Duncan discloses the sequential administration of a prodrug conjugate with an enzyme conjugate. The enzyme conjugate is administered in order to achieve overexpression of the enzyme at the desired site of release of the prodrug. In contrast, the claimed compositions contain a linker containing an oligopeptide recognition segment that is cleaved by a digestive enzyme that is overexpressed *by the tissue*. Duncan teaches away from the claimed compositions and methods since Duncan leaves the impression that one must co-administer an enzyme conjugate in order to achieve overexpression and cleavage of the peptide linker. Accordingly, one of ordinary skill in the art would not be motivated to combine the conjugates of Duncan with the oligomers of Copeland to arrive at the claimed compositions.

Secondary Considerations of Obviousness

Example 12 describes the *in vivo* evaluation of the anti-tumor efficacy of dextran-oligopeptide-methotrexate conjugates. Six week old female SCID mice were injected with HT-1080 tumor cells. Free methotrexate, dextran-oligopeptide-methotrexate, or dextran-methotrexate was injected intraperitoneally on day 1, 8, and 15 after a tumor was first established. Weight and tumor size were monitored three times a week. The average tumor size was suppressed 92% by the dextran-oligopeptide-methotrexate and dextran-methotrexate compared to free methotrexate. Linking methotrexate to a polymeric carrier, such as dextran,

increases the half-life of the drug by decreasing renal elimination rendering the benefit of passive targeting. The presence of a peptide linker containing a recognition segment promotes cleavage of the conjugate in the extracellular space of the tumor tissue where the digestive enzyme is overexpressed.

These results are unexpected in view of the teachings of Duncan which requires the co-administration of an enzyme conjugate in order for the drug conjugate to be effective and are strong indicia of non-obviousness.

Allowance of claims 1-6, 9-14, 17, 18, 21, 22, 29, 33, 39, 43, 44, 47-52, and 54-56, as amended, is respectfully solicited.

Respectfully submitted,

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